IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Application of Schwartz, et al.		
Serial No.	10/695,509	Examiner:	Fetterolf, Brandon J.
Filed:	October 28, 2003	Art Unit:	1642

For: METHODS FOR PREVENTION AND TREATMENT OF CANCER

DECLARATION UNDER 37 CFR 1.132

I, Gary G. Schwartz, Ph.D., M.P.H, Ph.D., the undersigned, am a citizen and resident of the United States, and hereby declare the following:

WHEREAS, I received a B.A degree in psychology from Pomona College in Claremont, California (1978); a Ph.D. in Biological Psychology from the State University of New York Downstate Medical Center in 1985 and, at the University of North Carolina at Chapel Hill, received a Master's in Public health in 1988, completed a Postdoctoral Fellowship in Cancer Epidemiology in 1989, and received a Ph.D. in epidemiology in 1993; and

WHEREAS, I have authored or co-authored more than 50 peer-reviewed research papers published in scientific journals and multiple abstracts, book chapters, and presentations in my field of expertise (a representative list of which is attached hereto as Appendix A); and

WHEREAS, I currently hold the joint positions of:

- Associate Professor (tenured), Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC; and

- Associate Professor, Department of Epidemiology & Prevention, Wake Forest University School of Medicine; and

- Scientific Director, Prostate Cancer Center of Excellence, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC.

WHEREAS, I previously held the positions of:

- Associate Professor, Department of Epidemiology & Public Health, University of Miami School of Medicine, Miami FL (June 1997-June 1999);

- Research Associate Professor, Department of Epidemiology & Public Health, University of Miami School of Medicine, Miami FL (August 1994-May 1997);

- Assistant Professor, Department of Clinical Epidemiology and Preventive Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA (May 1991-July 1994); and

WHEREAS, I am a named inventor on the subject patent application, and have read and reviewed the subject patent application, as filed and amended, as well as the instant Office Action and the references cited therein.

NOW THEREFORE, BEING established as an expert in the field of cancer research relating to the subject matter of the claimed invention, I make the following statements and render my opinion based on my knowledge of the inventions and in view of my experience and expertise:

THAT, the capability and the operability of the claimed physiological doses of 25-OHD3 to inhibit the proliferation of cancer or tumor cells, including prostate cancer cells, has been clearly demonstrated.

A scientific publication which clarifies the successful use of 25-OH Vitamin D3 to inhibit cancer cell proliferation is Lou, Y-R, Laaksi I, Syvälä, et al., "25-Hydroxyvitamin D3 is an active hormone in human primary prostatic stromal cells. FASEB Journal, 2004, Feb 18 (2):332-344", published online December 4, 2003. This Lou, *et al.*, publication is incorporated by reference into this Declaration, and a copy is being submitted herewith.

The Office Action cites certain references, namely, Ma, *et al.*, Hsu, *et al.*, and Whitlach, *et al.*, as showing that 1-OHase activity is reduced in prostate epithelial cells. Several authors, including those cited in the Office Action, have opined that the reduced activity of 1-OHase in these epithelial cells may make 25-Hydroxyvitamin D3 ineffective as a treatment for prostate cancer. However, as Lou *et al.*, teach, although several

papers have focused on the epithelial cells in the prostate, approximately half of the prostate is composed of stromal cells. The stromal component of the prostate "plays a critical role not only in the regulation of normal epithelial differentiation but also the progression of tumorigenesis." Lou et al. demonstrate that stromal cells from primary cultures of prostate cancer possess 1-OHase and that the administration of 25-Hydroxyvitamin D3 at physiological concentrations (100 – 250 nM), which is within the range claimed in the current patent application, reduces cell proliferation of these cells.

As background, Lou et al teach:

> "... epithelial and stromal cells are present in approximately equal numbers in human prostate and stromal cells are the first to face hormonal agents derived from the circulation. Thus, stromal cells may play a central role in the metabolism and action of vitamin D3 compounds in prostate organ. However, there is cumulative evidence that the prostatic stromal component plays a critical role not only in the regulation of normal epithelial differentiation but also the progression of tumorigenesis. Studies in vitro and in vivo have shown that prostatic fibroblasts can affect tumor cell growth and progression, the type and the extent of the response depending on both degree of malignancy of epithelial cells and pathologic extent of fibroblast origin. For instance, in the study by Olumi et al. prostatic fibroblasts derived from malignant human tissue were found to enhance growth, retard cell dealth and alter histology of initiated but not tumorigenic epithelial cells. Normal prostatic fibrobalsts have also been reported to reduce death of LNCaP cells [a prostate cancer cell line] in vitro coculture and in vivo xenograft systems. Hence, suppression or stimulation of prostatic fibroblast could affect cancer cell growth."

In their well-described paper, Lou et al show clearly that, using two human prostate stromal primary cultures (P29SN and P32S cells), "25-OHD3 was found at physiological concentrations of 100-250 nM to inhibit the growth of primary cultures" (Abstract). These findings are shown graphically in Figure 2 of their paper.

The authors conclude that the fact that 25-OHD_3 at physiological concentrations targets gene expression and suppresses cell growth in prostate cancer cells supports the view that this may represent "a potent anticancer therapy."

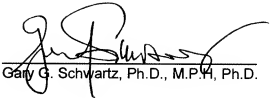
The demonstration of anti-tumor activity by 25-OHD shown by Lou, *et al.*, contrasts with the view expressed by Ma, *et al.*, that 25-OHD3 would be ineffective as therapy. As noted above, the view of Ma, *et al.*, is based on the reduced expression of 1-OHase activity in epithelial cells only. Ma, *et al.*, appear unaware of the findings of Lou, *et al.*, which were published prior to the work of Ma, *et al.*, in late 2004 (the online publication date for Lou et al was in December 2003, paper publication in February 2004), both of which carry publication dates well after the effective filing date of the subject application.

Notably, these experimental results provided in the Lou, *et al.*, publication establish a "clinical correlation" between the effective amount provided and the tumor or cancer inhibition, as claimed. Moreover, the experiments of Lou, *et al.*, were performed in primary cultures of cells obtained from individual men with cancer, and are thus cells within hours of being *in situ* and are a much closer model to the living individual than immortalized cell lines transformed from highly selected cells.

THEREFORE, it is my expert opinion that Lou, *et al.*, directly contradict the speculative conclusions of the cited Ma, *et al.*, Hsu, *et al.*, and Whitlach, *et al.*, references, and establish that cancer and tumor cells are inhibited by the physiological doses of 25-OHD3, as claimed.

I HEREBY DECLARE THAT ALL STATEMENTS MADE HEREIN OF MY OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENT MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE KNOWLEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER 18 U.S.C. 1001 AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE PATENT APPLICATION OR ANY PATENT ISSUED THEREON.

Further, Declarant sayeth naught.

Date: September 4 2009 By: 

Gary G. Schwartz, Ph.D., M.P.H., Ph.D.

APPENDIX A

PUBLICATIONS AUTHORED OR CO-AUTHORED BY GARY G. SCHWARTZ, PhD, MPH, PhD

Refereed Journal Articles

1. Cohen SW, Sherman M, **Schwartz GG**, Banko W, Cohen H, Mahl C. Lacrimal outflow patency demonstrated by chemiluminescence. Archives of Opthalmology. 1980;98:127-128.

2. **Schwartz GG**, Rosenblum LA. Novelty, arousal and nasal marking in the squirrel monkey. Behavioral and Neural Biology. 1980;28:116-122.

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14. **Schwartz GG**, Skinner HG, Duncan R. Solid waste and pancreatic cancer. International Journal of Epidemiology 1998; 27:781-787.

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16. Lokeshwar BL, **Schwartz GG**, Selzer MG, Burnstein KL, Zhuang S-H, Block NL, Binderup L. Inhibition of prostate cancer metastasis in vivo: A comparison of 1,25-Dihydroxyvitamin D (calcitriol) and EB1089. Cancer Epidemiology, Biomarkers & Prevention, 1999;8:241-248.

17. John EM, **Schwartz GG**, Dreon DM, Koo, J. Vitamin D and breast cancer risk: The NHANES I Epidemiologic Follow-up Study, 1971-1975 to 1992. Cancer Epidemiology, Biomarkers & Prevention 1999;8:399-406.

18. Barreto A, **Schwartz GG**, Woodruff R, Cramer SD. 25-Hydroxyvitamin D_3, the prohormonal form of 1,25-Dihydroxyvitamin D_3, inhibits the proliferation of primary prostatic epithelial cells. Cancer Epidemiology, Biomarkers & Prevention 2000;9:265-270.

19. Chen TC, **Schwartz GG**, Burnstein KL, Lokeshwar BL, Holick MF. The use of 25-Hydroxyvitamin D_3 and 19-nor-1,25-Dihydroxyvitamin D_2 as therapeutic agents for prostate cancer. Clinical Cancer Research 2000:6:901-908.

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32. Sahmoun AE, Case LD, Chavour S, Kareem S, **Schwartz GG**. Hypertension and risk of brain metastasis from small cell lung cancer: A retrospective follow-up study. Anticancer Research 2004, 24: 3115-3120.

33. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM, Kristal A, Santella RM, Probstfield JL, Moinpour CM, Albanes D, Taylor PR, Minasian LM, Hoque A, Thomas SM, Crowley JL, Gaziano JM, Stanford JL, Cook ED, Fleshner NE, Lieber MM, Walther PJ, Khuri FR, Karp DD, **Schwartz GG**, Ford LG, Collman CA. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Journal of the National Cancer Institute 2005, 97: 94-102.

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Book Chapters

1. **Schwartz GG**, Rosenblum LA. Primate infancy: Problems and developmental strategies. In: Wolman B (Ed), Handbook of Developmental Psychology, Englewood Cliffs: Prentice-Hall, 1982, pp. 63-75.

2. **Schwartz GG**, Rosenblum LA. Sneezing behavior and its biological significance. In: Handbook of Squirrel Monkey Research, Plenum Press, 1985, pp. 169-186.

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4. **Schwartz GG**. Chromosome aberrations. In: Hulka BS, Wilcosky TW, Griffiths JD (Eds), Biological Markers in Epidemiology. New York: Oxford University Press, 1990, pp. 147-172.

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